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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/584,216	FERBER, SARAH	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,9-13,15-17,24 and 26-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9-13,15-17,24 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application, filed May 31, 2000, claims benefit to provisional applications 60/137,143, filed June 1, 1999, and 60/198,532, filed April 19, 2000.

Applicant's amendment filed April 22, 2002, paper number 12, has been received and entered. The specification has been amended. Claims 3-8, 14, 18-23 and 25 have been canceled. Claims 2, 30 and 32 have been amended. Claims 1, 2, 9-13, 15-17, 24 and 26-32 are pending and currently under examination.

Election/Restriction

Applicant's election of group I, claims 1-17 and 24-32, in Paper No. 11 is acknowledged. Further, the election of species drawn to: (1) the nucleic acid which encodes PDX; (2) insulin as the hormone induced; and (3) intravenous route of delivery.

The election has been treated as an election without traverse in light of Applicant's election without prejudice to pursue non-elected claims in a later application, the cancellation of the non-elected claims, and because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement (MPEP § 818.03(a)). In light of the election of the polynucleotide which encodes PDX, upon reconsideration of the election of species for the route of delivery and hormone induced, it is reasoned that the instantly claimed method requires only expression of the nucleic acid and would not be affected by the route of delivery. Further, upon

delivery and expression of PDX the consequence on the cell, *i.e.* effect on any hormone expression, would be inherent to the expression and presence of PDX. Therefore, the election of species for these two groups is withdrawn.

Claims 1, 2, 9-13, 15-17, 24 and 26-32 are currently under examination as they are drawn to the delivery of a nucleic acid encoding PDX.

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). Specifically, the amendment filed October 19, 2001, paper number 7, in response to the notice to comply with sequence requirements, has been entered (the raw sequence listing has been entered as paper number 9). Upon review of the present specification and the sequence listing it appears that number of sequences correspond, however the specification has not been amended to reflect each of the specific SEQ ID NOs for each of the oligonucleotides disclosed.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Objections

Claims 1, 16, 24 and 29 are objected to because of the following informalities: It is noted the elected invention is drawn to delivery of a polynucleotide. Presently, the independent claims encompass delivery of any type of compound, not only a polynucleotide. It is noted that dependent claims have been amended to encompass a polynucleotide, however this elected limitation should appear in the first independent claim to limit all dependent claims to the elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 9-13, 15-17, 24 and 26-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing insulin, somatostatin, glucagon and prohormone convertase 1/3 gene expression in the liver of mammals comprising administering AdCMVPDX-1 in an amount effective enough to obtain PDX expression in the liver of said mammal, does not reasonably provide enablement for use of other delivery vehicles, inducing any and all pancreatic hormones, or providing a therapeutic affect to a subject. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 1, 2, 9-13, 15-17, 24 and 26-32 are drawn to a method for the delivery of a nucleic acid encoding PDX broadly encompassing any delivery route, any delivery vehicle (i.e. any type of vector and promoter), and increasing any pancreatic hormone. More specific claims encompass the same method but are drawn to treating a diabetic subject and specifically

increasing insulin. The specification and art teaches that PDX is a homeobox gene whose expression was previously described in pancreas and intestine, and taught to be associated with the development of these tissues (see Offield *et al.*, Dev 122:983-995 for example). The specification teaches that the instantly claimed method is based in part on the discovery that the expression of PDX-1 in the liver induces the expression of pancreatic hormone genes not normally expressed in the liver. Working examples demonstrate that administration of an adenoviral vector which contains the PDX-1 gene operably linked to the CMV promoter can increase the expression of several pancreatic hormones in the liver. The basis of the instant rejection focuses on the breadth of the claim for use of any vector system, the ability to induce expression of selective hormone levels in any tissue, and the use of the instantly claimed method to provide a therapeutic affect to a subject.

It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). In the instant case, the instant case the methods are generally drawn to gene therapy to affect the method as claimed.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). As noted above, at the time of filing PDX was known to be expressed in the pancreas and demonstrated to be important in the development of the pancreas (Ahlgren et al. Dev 122:1409-1416). Additionally, Ozcan *et al.* (BBRC, 295:724-729) demonstrated that PDX-1 transcriptional factor could bind to the A3 element of the insulin promoter and induce promoter activity in yeast (see summary in Figure 3, page 727). However, at the time of filing the art teaches that the ability of any particular cell to respond to the presence of PDX-1 is cell dependent and requires other factors for the effective expression of a gene which contains the binding site for PDX-1. For example, Marshak *et al.* (PNAS 93:15057-15062) teach that PDX, originally termed IPF and GSF in this reference, is differentially expressed in islet cells. Further, high levels of ectopic PDX inhibit the expression of the insulin gene (specific results in figure 6 and summarized in abstract). Conversely, Kajimoto *et al.* (J Clin Inv 100:1840-1846) teach that a decreasing the expression of PDX did not cause a decrease in insulin expression. Clearly each of theses references demonstrate that PDX alone is not responsible for the expression of the insulin gene, and that other factors are necessary for the effective expression of insulin. Seijffers *et al.* (Endo 140:3311-3317) describe the seemingly paradoxical expression of several nuclear factors known to affect the insulin promoter, and describe the cooperative role of the transcriptional factors necessary for the expression of the endogenous insulin gene. In total, the art teaches that for PDX to successfully affect the expression of insulin, other endogenous transcriptional factors must be present in the cell. The specification teaches that the present

invention is based on the unexpected result that PDX expression in the liver is capable of inducing pancreatic hormone expression. However, in light of the evidence of record for the importance of other factors besides only PDX, it is unclear that this unexpected result can be extended to any cell. Additionally, since the presence of PDX would potentially affect all genes in the cell, the specification fails to teach the necessary guidance for the selective expression of only affecting a single gene (claims 9, 26 and 30). Given the guidance in the present specification, the skilled artisan could not selectively alter the expression of a single gene of interest such as insulin, thus, one would not be able to use the instantly claimed methods for the treatment of specific conditions such as diabetes. The claims are broadly drawn to administration to a subject in need thereof, however the specification fails to define a subject which needs a general increase in multiple pancreatic genes or how to effectively control the expression of a single gene which would be required for treatment of a specific condition.

With respect to the use of any delivery system, at the time the invention was made, it is noted that successful implementation of gene delivery protocols was not routinely obtainable by those skilled in the art, in particular, the ability to specifically, predictably and reproducibly alter the physiology of a cell by the introduction of a polynucleotide. Verma *et al.* teach that as of 1997, "the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (p. 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (p. 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both

viral and no-viral, and poor gene expression after genes are delivered" (p. 30). The instant specification teaches that the use of AdCMVPDX can effectively increase the expression of several pancreatic genes in the liver. In the systemic delivery of adenoviral vectors, the predominant site of uptake of the adenovirus is in the liver. In light of the working example in the present specification it appears that the use of an adenoviral vector and the level of expression of PDX afforded by the CMV promoter results in adequate levels of PDX necessary to affect gene expression in the liver. However, it is unclear if other promoters which are not effective in the liver or which provide a different level of expression would be effective. As noted above, the art teaches that PDX alone is not responsible for insulin gene expression and that increased levels of PDX can actually decrease insulin expression under certain circumstances. It is noted that the instant invention is based in part on the unexpected result and in light of the art of record it is unclear that this unexpected result can be extended to any other tissue besides the liver, and to any other vector system besides AdCMVPDX. The specification lacks the necessary and specific guidance for the use and delivery of any other vector/polynucleotide, and thus, is subject to the same obstacles recognized by others skilled in the art as presented by Verma and Anderson.

Case law states that applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll,* 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be

required. *In re Fisher*, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." In the instant case, the disclosure of a single vector system delivered to the liver would not simply be extended to any other delivery system or any other cell type. Case law teaches *(Ex parte Forman*, 230 USPQ 546,547 (BPAI 1986)) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." In the instant case, the art teaches that the effect of PDX on a cell is not completely defined and is in part dependent of the cell and endogenous factors expressed in said cell. While the working examples provide evidence for the scope set forth in the basis of the rejection, the

specification fails to provide the necessary guidance to extend this unexpected result to other systems and other tissues for the expression of pancreatic genes.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 9-13, 15-17, 24 and 26-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1, 16, 24 and 29 is vague and unclear in what disorder is being treated. In light of the present specification, it appears that the expression of PDX induces the expression of pancreatic hormones in several cell types. However, simply increasing hormone levels would not appear to be a treatment and could be deleterious to a subject. Further, the recitation of "inducing" or "increasing" is unclear because the level of change is not clearly defined. The claims are framed in the context of delivery to a subject in need of increased PDX, however the claim does not clearly define what levels would be needed, therapeutic is said subject thereby being effective. For example, it is unclear how increasing hormone levels will be effective in treating pancreatic cancer. Further, while certain types of diabetic subjects may benefit from

increased insulin levels under certain circumstances, the increased levels should correspond to changes in diet, and is not a general need. The claim is unclear in defining a patient in need and what a therapeutic amount would be. The dependent claims are included in the basis of the rejection because they fail to clarify the basis of the rejection. It is noted that dependent claims include recitation of specific hormones and types of subjects and conditions, however, each fail to address the necessary limitations of when and how much polynucleotide should be delivered, and how to define a subject in need of the instantly claimed method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Milewski *et al.*

Claim 31 is drawn to a composition comprising a compound which increases PDX expression or activity in a pharmaceutical acceptable carrier. Milewski *et al.* teach several vectors which comprise the sequences which encode zebrafish and mouse PDX (bottom of page 1444). When the vector is administered to a cell, PDX is expressed and the increased activity of PDX activity in said cell is measured by promoter reporting construct (results summarized in

Figure 8, page 1448). Thus, the vectors containing the polynucleotide sequences which encode PDX which can be delivered to cells meet each of the limitations set forth in the claim.

Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Marshak *et al.*

Marshak *et al.* teach the identification and isolation of a glucose sensitive factor (GSF). Marshak *et al.* teach that GSF corresponds to insulin promoter factor 1 which is also known as PDX-1 (summarized in abstract, page 15057). Marshak *et al.* teach that a variety of factors affect the expression of GSF, among them high glucose levels are demonstrated to increase the expression of GSF/PDX and increase the promoter activity in reporter assays (see for example results in Figure 2). In light of the evidence that glucose increases the expression and activity of PDX, glucose would meet the limitations set forth in the claim.

The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Seijffers, R. *et al.* Endocrinology 140(7):3311-3317 provides further post-filing evidence that use of adenoviral vectors and expression of PDX-1 is deleterious to insulin production.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach

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